I N D E X

February 22, 2000

I N D E X (Continued)

KEYNOTE: "---" Indicates inaudible in transcript.

P R O C E E D I N G S

(8:35 a.m.)

WELCOME - OUTLINE PURPOSE AND OBJECTIVES OF WORKSHOP

DR. SUNDLOF: Good morning. If I could ask everybody to please take their seats, we can begin this morning's session.

(Pause.)

DR. SUNDLOF: All right. Good morning, everyone, and welcome to CVM's second workshop on antimicrobial resistance. It is really great to see the turn out that we have here today. For the next three days we are going to be discussing some issues that are very important to CVM and to the industry, and so, I hope everybody is refreshed and ready to go here.

The purpose of the meeting is to discuss the appropriate design of pre-approval studies. We talked about pre-approval studies for a long time in the context of antimicrobial resistance, and we need to consider in the discussion today both the rate and the extent of resistance development in the appropriate microbiological organisms and also look at the issue of pathogen load, which is also a critical factor in pre-approval testing.

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DR. SUNDLOF: So the meeting's objectives are to obtain scientific input on these issues. These are very complex issues that are meant to give us some kind of predictive value in assessing what will happen with the drug after the approval process.

And again, it is a scientific and complex issue, so we need as much as input as possible, and we would like to hear a lot of different perspectives and a lot of different alternatives hopefully that will emerge from this discussion.

(Slide.)

DR. SUNDLOF: Our goals are to get all the ideas out on the table. We want to hear as many as we can. We want to listen to our experts and ask them lots of questions. We want to hear from the public. We want to hear how they view some of the issues we will be dealing with.

We want to discuss these issues in further depth in the breakout sessions, which will occur tomorrow afternoon and Thursday morning. So the breakout sessions will give everybody a chance to participate in the discussion. And we want to do a lot of brainstorming. We want, again, people to come away from this with a greater understanding and appreciation than what they came here with. So lots of good ideas, hopefully, will emerge from this meeting.

I just want to make a statement right now that it is not the intention to come to a final decision on pre-approval studies at this meeting. This is not a meeting that is intended to reach a consensus opinion on what the exact proper study should be.

It is one in which we are going to try to get as many good ideas out as possible. Those ideas will then form the basis for further comment and finalization of what we will consider eventually as the proper design for these pre-approval studies.

(Slide.)

DR. SUNDLOF: Just to give a little bit of background, in November of 1998 we issued a guidance document, number 78, which says that based on what we perceive to be the potential public health threat from antimicrobial resistance development, we believed it is necessary to consider the potential human health impact of microbial effects associated with the use of animal drugs.

To do that, we were looking at two different issues. Resistance, and also, we wanted to consider pathogen load that may increase as the result of using antimicrobials. So that was guidance document number 78 in November of '98.

In December of '98 we issued a paper that we have referred to as the framework document, and I am sure everybody is familiar with that document at this time. It states FDA's position; that the regulatory system for antimicrobials for use in food animals should be modified to address microbial safety. Prior to that, with the exception of a few cases, we had not considered that in the assessment of safety.

The framework includes a concept of using pre-approval studies to evaluate the safety of the proposed products, and so pre-approval studies was a critical element in the framework document, and that is what this workshop is about; to really focus in on the pre-approval studies.

(Slide.)

DR. SUNDLOF: Just briefly, we will go through the agenda; what we can expect in the next three days. First of all, this morning we will have an overview of antimicrobial use patterns from a number of the producer organizations. So we will look at poultry versus ruminants versus swine, et cetera, and how antimicrobials may be used in those practices.

We will also hear a little bit about drug discovery and what is involved on the industry side on drug development. And finally, just to give everybody a solid background, we will have some presentations from people within CVM to explain the regulatory process in general, and specifically then, how it applies to the regulation of antimicrobial drugs for food producing animals.

We will also have a presentation based on what we refer to as "558.15" drugs, and those are the sub-therapeutic antimicrobials for which CVM has, for a number of years, required pre-approval studies. So that can serve as a kind of background for looking at what we have done in the past, where we feel the strengths of those studies were and where some of the weaknesses potentially lie. From there, it may be easier to try and move forward.

(Slide.)

DR. SUNDLOF: This afternoon we will finish session one. Again, there will be some talks from CVM people on the regulatory process, and we will have a discussion of some general concept of microbial safety and assessment. And we will be listening to some experts, some people that have got some experience and some ideas on how these studies might best be performed and the discussion of some of the specific factors to consider regarding resistance and pathogen load.

And then we will begin session two, which is more conceptual perspectives. We want to get different perspectives on how we might approach the issue of pre-approval studies for microbial safety. So on Wednesday morning then we will finish up those presentations.

And then, the people who have been talking this afternoon and tomorrow morning will sit on a panel and will have an open public meeting and a panel discussion tomorrow morning on some of the things that we have heard to date.

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DR. SUNDLOF: And then, on Wednesday afternoon, we will begin the breakout sessions. Those breakout sessions, if you look at your agenda, are grouped according to the species of interest. So they are species based breakout groups and people will be allowed to go to whichever of those breakout sessions that they feel is of most interest to them.

We have provided some questions, and they are in your agenda. The questions we won't go over at this time because a lot of those questions you really won't be able to have a good idea of how to answer until you have heard the discussions that have led up to the breakout sessions.

You will have an opportunity during the comment period on Wednesday afternoon to add additional questions or raise additional concerns for discussion during the breakout session.

(Slide.)

DR. SUNDLOF: Then, on Thursday, we will finish the breakout sessions and the chairs or the moderators of those breakout sessions will begin to prepare the reports. And then, on Thursday afternoon, we will have a presentation of all of the breakout groups and then further discussion, and then we will talk about next steps based on what we have heard during the course of the entire three days.

(Slide.)

DR. SUNDLOF: Okay. But it doesn't end there. It doesn't end Thursday. We still think that this is a continuing, ongoing process. It begins here, but it continues on, and we have opened up a docket and that is the number of the docket so that additional comments can be sent to FDA. That is the docket number that you refer to, and we will take all those comments into account.

Additionally, the transcript of this workshop will be made available. We will have a full transcript on CVM'S web site, and there you have our web site address. And then the final thing I need to do is just a few little housekeeping details.

Refreshments will be available during the breaks, but because we want to have as productive a meeting as possible, we would ask everybody to, please, try to return from the breaks on time so that we can keep on schedule. Lunches will be on your own. There will be a short reception on Wednesday at 5:30 in the evening.

And if you have any questions or need anything during the next three days, the two people that are sitting out there at the table outside of this room are Alita Sinderlar and Linda Cowatch, and they will be glad to assist you if you have any problems at all.

So, those are my opening remarks. I would now like to turn the program over to the moderator of the first session, and that is Dr. Claire Lathers. Dr. Lathers is relatively new in the Center for Veterinary Medicine. She is our office director in the Office of New Animal Drug

Evaluation where the studies eventually will be evaluated. So, Claire, I will turn it over to you.

CHAIRWOMAN LATHERS: Thank you, Steve. Welcome to the Center for Veterinary Medicine's workshop. We will be looking at pre-approval studies and asking the question: Antimicrobial resistance and pathogen load; how do we best design our protocols?

On behalf of the Office of the New Animal Drug Evaluation and the center, I would like to begin by thanking all of those who have contributed to the effort of making this workshop a success: Bill Flynn, Dave White, all of the members of the CVM pre-approval protocol group. They have spent a lot of time discussing possibilities, and now they are here to share and to listen with you and your ideas.

And Blue has assisted, Linda Towlson, Steve Sundlof, Sharon Thompson, and indeed, all of the senior management team. And finally, Anita Sinderlar and Linda Cowatch are the people that are making the actual workshop happen, if you would, in terms of the mechanics.

So, with the first speech, we will now begin our discussion of the appropriate designs for the pre-approval studies to evaluate the microbial effects of antimicrobial drugs intended for use in food producing animals and ask the question: How do we address the rate and the extent of resistance development and the changes in the number of enteric bacteria in the animal's intestinal tract that can cause human illness?

Our first speaker to begin to address these questions is Dr. Gates Riddell. He is a professor in large animal surgery and medicine at Auburn University, he is the past president of the American Association of Bovine Practitioners, he is a member of AVMA's drug advisory committee and a member of the AABP's committee on pharmaceutical and biological issues. Dr. Riddell.

ANTIBIOTIC USE IN RUMINANTS - AN OVERVIEW

By Dr. Gatz Riddell

DR. RIDDELL: Thank you, Dr. Lathers. I appreciate the opportunity to be able to bring some perspective from the ruminant species this morning. I would like to start off my comments by talking about some of the preparatory steps towards considering the use of antibiotics in ruminants.

There are numerous tools available to animal agriculture, which can be implemented to maintain animal health today. These include well-researched nutritional guidelines, vaccines both old and new to aid in the prevention of disease, a greater understanding of appropriate housing designs for various classes of animals and proven protocols for the integration of these tools in preventive medicine programs.

However, there are also numerous uncontrollable variables which can impact animal health and which can compromise the effectiveness of health maintenance protocols. Antibiotics are and will continue to be an important and necessary tool for the treatment of certain infectious diseases and prevention of pain and suffering resulting from these diseases.

It is difficult, if not impossible, to prevent exposure to disease pathogens. For example, the bacteria, group of bacteria, that have been associated with causing bovine respiratory disease.

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DR. RIDDELL: Some of these infectious agents are found in regionally select areas of the United States. Others may require the presence of specific animal populations, while others may be universally found in the environment, regardless of the presence or concentration of animal agriculture.

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DR. RIDDELL: Variables which can place animals at risk for developing disease subsequent to exposure to these bacterial pathogens include variation in individual animal susceptibility to disease and response to effective vaccination protocols. There will be environmental stressors that are truly uncontrollable, such as weather, drought and other ambient conditions.

There will be life cycle events that are stressors of themselves, such as calving in lambing for the yew, and there will be management stressors, such as diet changes, which are important as we take this monogastric animal at birth to a ruminant at maturity, and transportation.

In addition to the potential for bacterial pathogens to cause disease, there are numerous viral agents which can alter local or systemic immune system function and open the door for secondary bacterial infection.

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DR. RIDDELL: For those diseases of bacterial origin, the only recognized therapy may require the use of properly selected, dosed and administered antibiotics. It is impossible within the scope of this short presentation to describe all the diseases scenarios for which the use of parenteral,

(Slide.)

DR. RIDDELL: Invasive surgical procedures will be performed on ruminant animals under field conditions which can place the animal at risk for bacterial wound infections. Examples of some of these field procedures would include exploratory abdominal surgeries and cesarean sections performed because of obstetrical difficulties encountered in an animal which cannot be transported to a surgical facility.

Beyond that, even excellent surgical facilities themselves cannot prevent all bacterial incisional complications. Additionally, ruminant animals may, by their nature, suffer traumatic injuries which can be complicated by secondary bacterial wound infections.

The former circumstance, surgical procedures, will require systemic antibiotics to prevent bacterial infection following contamination, and the latter, the traumatic injury, may require a full return to health following the development of a bacterial infection.

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DR. RIDDELL: There are certain conditions under which the potential for the development of a bacterial infection is increased due to environmental transport, management, housing or life cycle circumstances. Respiratory disease in cattle or lambs entering the feed lot are an example of this.

As with many diseases seen in agriculture, the causes of respiratory disease outbreaks are considered truly multi-factorial. The stress associated with transportation and increased exposure risk due to the commingling of newly introduced and the potentially immuno suppressive effects of at least one upper respiratory virus all tend to predispose to bacterial disease.

Now, there are numerous antibiotics on the market today which are labeled for treatment of bovine respiratory disease, each of which can be effective against the disease, but none of which will be universally effective. Therefore, the need for the current armamentarium and increasing our armamentarium in this area.

For this reason, the wide range of therapeutic options will allow a practitioner to base treatment upon diagnostic microbiology and previous experience, with clinical judgment thrown in, and make treatment adjustments where needed.

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DR. RIDDELL: Another bacterial condition which is life cycle related and which will respond to antibiotic therapy is a life-threatening uterine infection, which develops in the first three to 10 days after a cow has a calf. This condition, known as a toxic or septic metritis, can make an animal severely ill, may result in her death or render her reproductively unsound in future years.

In years past, intrauterine antibiotic therapy has been utilized, to a great degree, to treat this condition. Research on the type and location of problematic bacteria now suggests that systematic antibiotics, rather than intrauterine, are markedly more effective.

Monitoring protocols have been developed and implemented on many herds to develop infections early in the stage of the disease, which involves something as simple monitoring, daily, the body temperature of the animal.

These protocols have been able to direct much more specific and limited antibiotic use because of early intervention. These use of these protocols allowed treatment to be initiated earlier in the disease in those animals which are going to develop metritis, thereby enhancing the therapeutic success rate and minimizing the overall use of antibiotics because of early intervention.

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DR. RIDDELL: Lameness is a common condition diagnosed in both beef and dairy cattle. There are specific bacterial conditions, such as necrotizing pododermatitis, a condition commonly known as foot rot, which occurs when certain types of anaerobic bacteria gain entry into the soft tissues of the lower leg and feet of cattle. These infections respond readily to the use of appropriate systemic antibiotics.

More common causes of lameness are conditions such as sole bruises and sole ulcers, as you see in the picture here, for which antibiotic therapy is of little benefit or no benefit. Diagnostic and treatment protocols for lameness in cattle have been developed which direct therapy to the specific condition, including antibiotics where necessary and appropriate.

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DR. RIDDELL: Trained, experienced veterinary practitioners are able to evaluate disease outbreaks, apply well researched principles and make predictions as to when disease outbreaks may potentially spread to other unaffected animals. An excellent example of this type of outbreak is bovine respiratory disease.

The multi-factorial nature of this disease and the many predisposing factors have already been outlined. When the predisposing factors are present and unaffected animals have been placed at risk, the metaphylactic or prophylactic use of antibiotics in cattle and feeder lambs at risk for the development of respiratory disease of bacterial origin can prevent the outright development of disease in large populations of animals.

Studies have demonstrated that the appropriate application of the principles of metaphylactic therapy can reduce the overall use of antibiotics in certain groups of animals.

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DR. RIDDELL: Another example of a preventive strategy which involves the use of antibiotics would be the use of intramammary antibiotics in the dairy cow entering the dry period, a time in her life cycle in which there is a documented increase in risk for the development of bacterial mastitis.

When a mature lactating cow reaches seven months of pregnancy, she is dried off and she enter her dry period. This is a time where she is not milked to allow regeneration of the secretory cells of the mammary gland before she enters her subsequent lactation with the birth of her next calf.

The two times that you can see on this graph of greatest risk for the development of a new intramammary infections during the entire lactation cycle are the first two weeks and the last two weeks of the dry period. In addition, lactating dairy cows may enter the dry period with a subclinical bacterial mastitis.

It has been well established that the infusion of antibiotics into the mammary gland at a time when the cow will not be milked for 60 days enhances udder health and promotes the production of higher quality milk in the subsequent lactation. The high risk period found at the end of the dry period, on the other hand, is more appropriately mediated by the use of vaccinations, where appropriate, housing and environmental upgrades and nutritional programs directed toward maximizing the performance of the immune system.

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DR. RIDDELL: Very young calves, two to 10 days of age, may encounter chance overwhelming systemic bacterial infections, typically with Gram negative organisms. The only treatment which will enable this young class of animal to overcome the bacterial infection found within the blood stream will be systemic antibiotics specific to the suspected organisms.

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DR. RIDDELL: The practice of feeding antimicrobials, such as the ionophores, which alter ruminant flora populations, to enhance preferential development of -- production of volatile fatty acids to promote efficiency. Bambermycins, tylosin, virginiamycin and tetracyclines enhance growth promotion, enhance feed efficiency and work towards disease prevention, resulting in improved animal performance, productivity and efficiency.

There are numerous label indications for antibiotics in the feed. These include increased rate of gain, improved feed efficiency, the prevention or liver abscesses and the control and treatment of anaplasmosis.

The prevention of liver abscesses and the control of anaplasmosis directly impact animal health and well being. Other methods of control of these two conditions are limited or non-existent. The well proven decades old vaccine for anaplasmosis has been off of the market for several years.

The use of fed antimicrobials to enhance rate of gain and feed efficiency results in more efficient animal protein production, more effective use of feed grains and more responsible nutrient utilization in terms of waste management.

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DR. RIDDELL: As I mentioned in the beginning, it is very difficult to define, in the limited time available, all potential uses of antibiotics in ruminants. Hopefully, I have stimulated some thought and provided some framework for discussion by some of the representative examples I presented, and hopefully, discussion over the next three days will help further explore these uses and answer questions pertaining to this topic.

In summary, antibiotic use in ruminants is necessitated when the variables involved in animal agriculture, such as environmental conditions, chance exposure to infectious agents and variations in individual animal susceptibility predispose to individual animal disease or outbreaks in herd populations. The proper evaluation, thorough diagnostic procedures and the implementation of appropriate therapies, particularly under the auspices of a valid veterinary client patient relationship, when appropriate, will enhance the efficacy and safety of the use of antibiotics in ruminants. Thank you.

(Applause.)

CHAIRWOMAN LATHERS: I think we have time for one question, if someone would like to ask a question.

(No response.)

CHAIRWOMAN LATHERS: Our next speaker will be Dr. Dennis Wages. Dennis is currently a professor of poultry health management at the College of Veterinary Medicine at North Carolina State University. Dennis earned a bachelor of science in poultry science at the University of Arkansas, a doctorate of veterinary medicine at Kansas State University, completed a pathology residency at Iowa State University and is currently at diplomat status with the American College of Poultry Veterinarians. Dr. Wages.

ANTIBIOTIC USE IN POULTRY - AN OVERVIEW

By Dr. Dennis Wages

DR. WAGES: Thank you, Dr. Lathers. Good morning. I have been asked to give an overview of antibiotic use in poultry, probably one of the areas of most controversy in the use of antibiotics in food animals, and hopefully, I can give you an idea of why we do what we do and some of the thinking that is involved in the utilization of antibiotics.

I will touch base on therapeutics in the water, therapeutic feed grade antibiotics, growth promotion and the use of injectables in the limited time that I have.

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DR. WAGES: Antibiotic use in the poultry industry has been a fundamental intervention strategy since the 1960s. Even though preventative disease management is the primary focus of the industry's disease control, and we maintain much emphasis on vaccination protocols and the study of immunology, disease outbreaks that do occur, and it is a fact of life that it requires antibiotic therapy in some cases.

The majority of antibiotic treatment in poultry for acute disease outbreaks occurs via the water route. When a disease is identified within a flock, morbidity and mortality are assessed, necropsies are performed and a diagnostic evaluation is initiated in the diseased flock.

When culture and antibiotic susceptibility profiling has been performed, the veterinarian considers farm history, previous diagnostic evaluations specific to that farm and in that area and initiates appropriate control measures, which does include environmental and management changes, as well as, in some cases, the use of antibiotics.

We currently have eight classes of antibiotics used for water administration, and they represent 15 antibiotics that are approved for use for the treatment of acute bacterial diseases in poultry. They are dosed based on milligrams per kilogram of body weight -- that is, the pounds of meat in the house -- at labeled indications or based on the veterinarian's clinical judgment.

Any use of antibiotics not in accordance with the label indications are to be done within the guidelines outlined by AMDUCA. The antibiotics commonly chosen for use in appropriate disease outbreaks as intervention tools for water administration include the tetracyclines, streptomycin, neomycin, bacitracin and penicillin. These antibiotics represent tools that we use. We don't treat a lot. But when we do, these are the ones that are used more commonly.

Antibiotics that are less routinely or commonly chosen include lincomycin, streptomycin, tylosin, erythromycin and sulfonamides. These antibiotics are used. The latter group are used in the industry; however, they are used to treat diseases that we don't say on a day-to-day basis. You could take probably eight percent of our treatment for acute outbreaks and lump them into E. coli bacillosis and falcollera (sic) in turkeys and chickens, and that is the majority of what we treat for.

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DR. WAGES: The fluoroquinolones are used at labeled indications. They are not used in any extra label format, in that it is against federal law to do so, and they are used sparingly in our industry. They are cost prohibitive. It is not uncommon to put $1,500 into a flock of chickens with the use of the fluoroquinolones, and it is just not cost effective to utilize such treatments when you look at a cost per pound benefit. It is a very important drug to our industry.

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DR. WAGES: A survey of the National Chicken Council places fluoroquinolone use somewhere between one and two percent in the broiler production. We try to hold it in reserve. The fluoroquinolones currently represent the only drugs consistently effective for coli bacillosis in turkeys and chickens, and that is our number one disease.

Because of the economic impact of disease in poultry, disease prevention through rigid vaccination protocols and management improvements are emphasized while veterinarians in integrated companies closely regulate treatments. No, we are not perfect. Companies that have used antibiotics excessively and inappropriately instead of utilizing stringent disease prevention programs are simply no longer in the poultry business. They can't afford to be.

The aforementioned antibiotic intervention tools are used in specific diseased flocks regarding specifically diagnosed bacterial infections, and we do not use antibiotics in healthy flocks. However, in a house of 25,000, when a disease such as coli bacilloses occurs and we are losing five to seven birds per thousand, we do have a number of birds that we call at-risk that are not diseased and appropriate antibiotics are used in the diseased house. But, in fact, there are birds that aren't sick at that time in a prophylaxis use of antibiotics. Long-term therapy for chronic infection is not cost effective, nor is it performed in the poultry industry.

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DR. WAGES: Growth promoting antibiotics are added to the feed primarily as a control measures for common enteric bacterial diseases, specifically clostridial infection that result in necrotic enteritis. History has determined growth promoting antibiotics and their use to be sub therapeutic, a term that has been used against the poultry industry and the food animal industry for years and a term that I personally feel is inappropriate, and I will try to explain.

If one looks at the definition of therapy and treatment, there is, under all the definitions in Dorland's Medical Dictionary, areas where prophylaxis and prevention are identified as tools in the treatment and initiation of therapy. The reason sub therapeutic was adopted years ago to describe growth promotion can be explained in my mind.

In poultry, sub-clinical infections with coccidia in commercially raised flocks predispose birds to necrotic enteritis. Even though the anti-coccidial feed additives are routinely and were routinely used in commercial poultry, antibiotics such as virginiamycin, bacitracin and lincomycin were added to the feed to prevent necrotic enteritis infections due to Clostridium perfringes.

These antibiotics were needed because the coccidia preventative feed additive to control coccidiosis were static and not cidal, thus preventing clinical coccidiosis in the flock, but not preventing sub clinical infections and the protozoa proliferation within the intestines that predisposed the bird to necrotic enteritis infections.

Since the levels used in the feed of these antibiotics to prevent and control necrotic enteritis were lower than those used to treat active, acute outbreak of enteric they were coined sub therapeutic; below the therapeutic dose needed to treat an active infection. Even though we did control infection. A perfect example is 50 grams per ton of an antibiotic would control necrotic enteritis. If they broke with the disease, it would take 400 grams per tone to treat an active infection within a five to seven-day period.

I don't think in today's terminology sub therapeutic is appropriate, although it is very coined and people are very comfortable with it. Today, we still use virginiamycin, bacitracin, lincomycin and bambermycin to prevent and control necrotic enteritis and for growth promotion; however, since the 1980s -- in fact, about 1982 -- the poultry industry has not used the tetracyclines, penicillin, sulfonamides or erythromycin in feed for growth promotion or at low levels for disease control.

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DR. WAGES: Besides disease control, antibiotics have other modes of growth promotion, some known and many unknown. Certain antibiotics used in poultry increase chilled and hot carcass weight, improve breast yield and have protein sparing effects in the intestines. Many of these growth promoting mechanisms and results can be attributed mainly to control of sub clinical disease, such as necrotic enteritis, and some mechanisms specifically are unknown.

Some growth promoting antibiotics increase intestinal tensile strength, the strength of the intestine. This intestinal health and tinsel strength is important not only for the overall health of the bird, but also as an advantage at the time of processing to prevent bacterial contamination.

It has been demonstrated that certain antibiotics increase tinsel strength and intestinal integrity that prevents the tearing of intestines during the automated evisceration process. This helps prevent contamination from intestinal breaking at processing, which decreases the bacterial load at processing on our carcasses.

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DR. WAGES: Besides overall disease reduction and other cost benefits, growth promotion increases feed utilization by decreasing the amount of feed required to produce one pound of gain. To put this in perspective, if feeding an antibiotic to control necrotic enteritis or to improve growth promotion and feed efficiency would increase the efficiency 0.01 or 100th of one pound, which would reduce feed conversion from a 2.00 to 1.99. This represents a savings to our industry in the feed utilization of 375 million pounds.

This reduces the amount of grain required to furnish this feed, reduces electricity and the milling, or to mill this feed, reduces gasoline to deliver this feed. It is a snowball and domino effect on reducing the cost for a chicken.

Enhanced feed utilization also reduces fecal nitrogen and phosphorous excretion in litter, thus is an environmental advantage when applying litter to pastures and crops, another point that is of concern in intensive livestock grazing areas.

Growth promoting antibiotics or any other use of antibiotics are not used to treat poor management. Antibiotics simply do not replace deficiencies in management, despite popular press.

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DR. WAGES: Antibiotics added to the feed are rarely used to treat acute disease outbreaks. Now, this is feed grain antibiotics for acute outbreaks of disease. Antibiotics that are approved for use in this manner include the tetracyclines, erythromycin, bacitracin, tylosin and sulfonamides. And all of my list of antibiotics may not be entirely complete, but I think they are the ones that are the most common.

These products are difficult to use in the treatment of an acute outbreak routinely. It requires the removal of coccidiostat from the feed or requires a cross clearance with the commonly used coccidiostat during treatment, and either removing the coccidiostat or trying to find cross clearances and have companies put their money into cross clearances, none are very palatable to the industry at this time.

There are cases, such as chronic fowl cholera in breeders and some Mycoplasma species infections where pp. infections where feeding a feed grade antibiotic at a therapeutic intervention level for 10 to 14 days may be cost effective and potentially reduce condemnations at processing, but this procedures is rare.

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DR. WAGES: Injectables. There are antibiotics approved for use as injections in day old chickens and turkeys to control omphalitis or yolk sac infections. This procedure has been performed for over 30 years in the poultry industry.

Now, in the incubation process, at approximately 19 and 27 days of age, in chicks and poults respectfully is taken from the outside of the chick or poult and drawn into the body cavity. This period of time is a window of opportunity for bacteria to enter the developing embryo.

Until 1993, yolk sac infections in chickens were controlled with the injections of antibiotics such as gentamicin and spectinomycin at 1 day of age. In 1993, with the approval of Marek's disease in ovo vaccination, which basically vaccinates for Marek's from the time that chickens are transferred from the setting incubators to the hatching incubators. This process was approved.

This in ovo technique also provided a window of opportunity for an injection of antibiotic at the time of vaccination for Marek's that would try to and at least potentially more effectively control the yolk sac infection by placing the antibiotic at the point of contamination when the yolk sac is withdrawn into the body cavity.

If the bacterial contamination occurred at any point during the egg collection, storage and incubation of the eggs in ovo antibiotics, in our mind, felt like there was a benefit to the chick in controlling bacterial yolk sac infections.

Now, the only antibiotic approved for such injection is sarafloxacin, a fluoroquinolone. And I will tell you that it is not and has not -- and we kind of snubbed sarafloxacin. We do not use it in day old in ovo injection, nor in any other procedures of injections in poultry. Sarafloxacin injectable, in the poultry industry's mind, is predominantly a dead issue.

The poultry industry felt that fluoroquinolones were too important to be used as a day old preventative or control for yolk sac infection or omphalitis.

The two most commonly used antibiotics for in ovo administration are ceftiofur and gentamicin. These are not approved for in ovo administration. They are used under AMDUCA as extra labeled.

Although stringent cleaning and disinfecting of hatcheries and hatchery equipment are performed daily, these procedures cannot prevent some bacterial contamination from the egg collection and storage process. The use of antibiotics in chicks and poults and/or in the developing embryo provide the poultry veterinarian a useful tool for controlling yolk sac infections in chicks and poults during the first week of life.

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DR. WAGES: Antibiotic intervention in poultry is a tool. It is one tool in a total disease prevention program that emphasizes preventative disease management and vaccination protocols, et cetera. We simply can't afford to have disease in poultry flocks and maintain our current cost per pound benefit of production.

Our industry does not encourage nor endorse indiscriminate use or excessive use of antibiotics in our flocks. Currently, the American Association of Avian Pathologists Committee on Drugs and Therapeutics, which I am currently the chair, are drafting specific guidelines to promote judicious use of antimicrobials in poultry to preserve the efficacy of all antimicrobials in both poultry and human medicine.

And I assure you we are looking at all ways that we use antibiotics and determine whether we are doing things in the most effective way and what impact we have. We are convinced that what we do in poultry medicine and in our food animal species regarding poultry no longer just impacts the poultry and the growers and the companies. The impacts are global.

This effort supported by the American Veterinary Medical Association and the AVMA Committee on Judicious Therapeutic Antimicrobial Use. This will provide the front line poultry veterinarian in poultry to continue to make informed decisions regarding poultry intervention strategies. Our antibiotic arsenal is small, but when the need for antibiotic use is warranted, we need to have access an appropriate therapeutic avenue.

This overview is kind of short. Hopefully sweet and to the point. It doesn't, I am sure, answer all the questions. I hope that it at least does explain some mechanism and things that we do; why we do. I am sure it won't satisfy everyone, but if there are any questions, I would be happy to take them now. Thank you very much.

(Applause.)

CHAIRWOMAN LATHERS: Are there any questions for Dr. Wages?

(No response.)

CHAIRWOMAN LATHERS: If not, thank you very much.

DR. WAGES: Thank you.

CHAIRWOMAN LATHERS: The next speaker is Dr. Robert Morrison. Bob is an associate professor at the College of Veterinary Medicine at the University of Minnesota. He is director of Pig Champ, a software business serving the swine industry, he is a co-owner of a 2,000 sow multiplication herd, he is a board member of Allison Meats, a regional meat produced and processor, he is vice president of the American Association of Swine Practitioners, and, as such, he works closely with veterinarians and has a broad experience which combines both applied science and business aspects in terms of pork production.

You will now hear his presentation on antibiotic use in swine. Dr. Morrison.

ANTIBIOTIC USE IN SWINE - AN OVERVIEW

By Dr. Robert Morrison

DR. MORRISON: Thanks very much. I am going to just giver an overview of how veterinarians approach the treatment decision within swine facilities, and I would like to thank the committee for asking the American Association of Swine Practitioners to be here.

(Slide.)

DR. MORRISON: What I was led to believe at least is that many of you here maybe weren't all that familiar with pork production, and so I put this slide in just to show you a representative barn. Not, of course, a barn that all pigs go through like this, but not a atypical barn that a lot of pigs might go through in terms of their growth process.

And so what you can see here is a barn that might have 1,000 or 1,200 pigs in it, and they would be all relatively similar in age and weight. They probably came from one sow barn, and they came into this facility let's say around eight or nine weeks of age and they are going to stay here for three and a half months or so, at which time the barn -- again, if this was an example barn -- would be emptied and all of these pigs would go to market.

The barn would be completely washed down with a power wash and hot water disinfectant, and basically, the next group of pigs that would come in would come into the equivalent of a new basically disease-free, if you think of that way, barn. And that sort of production is what we try to produce pigs through in a way today so the new group that comes in has a new chance to do well.

So that is not an atypical barn, as I said. That would be called a naturally ventilated barn. So you have got curtains on the side, and you can see the curtain on the left side there is open, letting light in. On a hot summer day the curtain on both sides will be open, and you will get nice ventilation going through.

Now, what you can also see there is that those pigs have plenty of opportunity for touching each other; nose to nose contact, oral fecal contact, and so there is quite a bit of opportunity for transmission of infectious agents. And so, when something gets in there, it is very likely to spread if you don't have sort of the set up right to try and do things right.

(Slide.)

DR. MORRISON: Now, if you think of that barn, I would like you to just ask yourself which of these three is it most similar to. Is it most similar to a daycare facility or a residence at a small liberal arts college or a nursing home? And you could argue which one it is most similar, but what I am going to propose today is that it is most similar to a residence where you have got a group of relatively --

let's say mature individuals, hopefully mature, coming and they are going to stay there for a while.

And they are not going to come in and go, like in a daycare where you are going to go home, bringing new infectious agents back every day. Anybody who has got kids at daycare you know you are sick virtually every other day.

In a residence, however, you are going to come and you are going to stay and you are going to stay there for eight months and then you are all going to go home and the residence is emptied. The other important part about that residence versus the other two is that they are immunologically mature.

They are not like a daycare facility where babies don't have a well developed immune system let's say or not well exposed. They are not like a nursing home where you have got perhaps immune compromised individuals, people who cannot withstand infection. These pigs in this barn are physiologically and immunologically mature, and they are going to stay there. They are going to respond well to vaccines, et cetera.

I say there at the bottom, "We must consider the population when treating a disease." We have those 1,000 pigs in there and maybe three of them today are sick, but 997 are at risk. So that is very important to us when we think about the treatment decision for a barn.

When I am teaching veterinary students, I will have 70 students in the class let's say. And on a bad day in February, 10 will be absent from flu virus, 15 should be absent because they are, you know, sniffling, they are dripping, they are shedding quantities of virus into the air that infect the professor, 15 of them are probably feeling kind of rotten and the other 30 are pretty good.

That is the same situation when we have that barn with 1,000 pigs in it. If you have something break with it today, a few are going to die. Some are going to be quite clinically sick, and we want to, hopefully, turn those around. Maybe half of them are at risk of getting sick, and maybe 30 percent of them are going to do absolutely fine.

(Slide.)

DR. MORRISON: So, when we treat or not, a veterinarian, intuitively, is going to go through these sort of decisions. What this particular disease costs in that 1,000 pig barn. What that disease costs. If it costs nothing, I am very likely not going to do anything.

The impact on the pigs' well being of that particular disease; how does it affect their well being. So we may have some diseases that maybe don't have a huge cost, but they may affect the well being of some individuals, and we may decide to treat on that.

What will likely happen if I ignore it? Will it go away? You know, the vast majority of infections that take place just go away on their own. And fortunately, for veterinarians we ride the descending curve, if you remember your veterinary school of animals and individuals getting better. Some will stay the same or some will get worse.

The cost of the proposed management changes in treatment. That is one of the things we are going to always weigh. What is this going to cost, the scenario that I am treating, versus what is it going to cost for my recommendation. And hopefully, my recommendation saves money. And the likelihood of resolving the problem with these changes in treatment. So, some probability of success.

And by the way, all of these slides are going to be available, I think, to all of you. So you don't need to copy this down.

So, those are the intuitive decisions that veterinarians go through when he or she is going to recommend treatment. Now, some folks have put these into very elaborate spreadsheets, and they are very nice tools for deciding whether to treat or not.

(Slide.)

DR. MORRISON: We diagnose a problem by the following: We are going to look at records. More and more today pig production is based on very elaborate and detailed record systems, and so we are going to look at records. We may have feed consumption, water consumption, weight gain curves, as well as mortality. Maybe we have a coughing index. Somebody goes in and measures coughing. So we have got a lot of records to try to figure out what is going on in that barn of 1,000 pigs.

We will have clinical signs obviously in history. We have got veterinarians who are trained for many years to figure out what is this picture telling me. We will have serology done both on cross sections in some cases and serial bleeding. In other words, we will bleed pigs over time to figure out are they sero converting to agent "x."

And then we will have postmortem on both pigs that die, and sometimes we will sacrifice representative pigs and try to figure out what is happening in the population here. And we will have some pigs that we will sacrifice and do a postmortem in order to figure out what is going on in the other 999.

(Slide.)

DR. MORRISON: Now, despite that sort of elaborate protocol that we will have to try and figure out what is going on, we have some systems that -- like here is a farm that has a problem, and you can see each dot there is a group of 1,000 pigs. And the "xx" that is down at the bottom is time. And the "y" axis, by the way, is mortality.

So assume for the moment that every dot is 1,000 pigs, and you can see that way back in '96 they had roughly, you know, one percent. Down at the bottom left you can see we are down around one percent, two percent mortality. And over time, what you see here is that this mortality is going up, and, of course, that is very disconcerting to the owners, very disconcerting to the veterinarians -- their jobs are on the line -- and they are spending a lot of money to try to figure this out to make this curve go down.

But this is a very frustrating case. You can also note, for those of you who are unfamiliar with finishing, we like to have mortality down two percent or lower. You are always going to have a few die that just -- whatever. But we like to have it down in this one, two percent range. That is a nice, well run barn.

But when you are getting up here in this five, six, seven percent, you can see that this is also very unpredictable. This is just a nightmare for these folks to try and figure out what is going on and how to fix it.

(Slide.)

DR. MORRISON: In that graph what I was showing you was mortality, and something that we teach and emphasize a lot is that mortality is probably just the tip of the iceberg and underneath that. So we said we will tolerate one, two percent mortality. When you get up three, four, five percent mortality, what you have got is a lot of pigs that are going to become sick and need to be culled. Or at least they are going to go to market light than what we would like. Okay? And that is a loss.

And then, furthermore, you have got pigs that are growing slower. This top group there, some of those will go to different market, like a light market in town where they consume pigs that are much lighter than most of those. The greater majority of those are going to go to market light, and they are going to cost me an enormous amount of money. So mortality is just the tip of that iceberg when it comes to cost of the producer.

And so, I have got my barn of 1,000 pigs and let's say only four percent are going to die, and I say only in quotation marks. But 96 percent of them are affected, and so that is very, very important when I make my treatment decision.

(Slide.)

DR. MORRISON: An important point for me is that treatment is a short-term expense. Every time I add a treatment, it costs money. It takes money off the bottom line. So I don't want to treat any more than I need to, but you weigh that against management change. If I can go in and take that last graph where that line was going up, every group of pigs there is probably going to require some sort of treatment. That is an expense.

Now, I am going to weigh what can I do in that system or that barn as an investment to try to change that, to try to turn that curve around. So management is going to be viewed as a long-term investment, and I am going to look for some return on the investment.

And you can see here that we might look for changes in housing, we might change the way by which pigs flow, we might change the health of the incoming stock and lastly, at the bottom, we might change feed and water supply. All of those are going to cost, depending on the size of the farm, hundreds of thousands, perhaps tens of thousands; perhaps millions of dollars.

I will give you an example, a recent example looking at some numbers from a farm system. They have looked at groups that go through barns that have natural ventilation. So the curtains are open; nice summer breeze coming through. They have looked at those versus groups that go through with mechanically ventilated barns. So you have got fans exhausting air and controlled inlets letting the air in.

They have determined that in the groups that have the mechanically ventilated barn they have roughly about .8 percent lower mortality than the groups that go through with curtain ventilated barns, and they said, well, we have to look.

If we have curtain sided barns, we know that we are going to have higher mortality, we are going to have poor feed efficiency, we are going to have lower gain, we are going to have more expense for treatment, so let's ante up. And they are actually spending -- I think it is $20,000 per barn to change it over to a mechanically ventilated barn so that they can reduce the cost and they can improve the performance on every group that goes through there.

So that is a management change that they will try and impose across all barns, such that they reduce the treatment expense.

(Slide.)

DR. MORRISON: The treatment program is selected based on these following criteria: And Dennis gave you a nice summary of actual treatment that the poultry business uses. I am not going to go through drugs, but they all will follow this sort of a regime.

What is my diagnosis? And it is a best guess. Hopefully, it is an educated best guess. Hopefully, it is right. But what is my presumptive diagnosis? What do I know about this herd historically? What is the prevalence and incidence of this disease? Do I need to treat at all? Is it just one pig in the 1,000? And the incidence. How many new pigs are getting sick every day?

Will the owner do or will the staff do what I ask them to do? A common cut off let's say is in the 10 or 20 percent range of infected pigs or affected pigs that need treatment. If more than 20 percent are infected and affected, I probably am not going to get that owner or staff person to go in and inject pigs. It is just too big a task.

And so, if I say, listen, it is really cheap if you will just go in and inject these 250 pigs once a day for three days or twice a day for three days, forget it. You know, the staff person who is getting $8.00 an hour isn't going to do it.

So I may have to go in and water medicate. Or, in some cases, as we will see, I may have to go in and feed medicate, because I can't get them to do what I think they ought to do, from a compliance point of view.

Benefit costs of treatment options. I am going to think about that. I am going to look at my lab results. I am going to weigh, obviously, my clinical experience and the antibiotic options available. All of those are the criteria that I am going to consider.

(Slide.)

DR. MORRISON: Now, I just want to -- there is a very detailed treatment set of guidelines that the veterinary employs when choosing a treatment. I just want to go over these very quickly.

(Slide.)

DR. MORRISON: First, the veterinarian is going to decide, well, am I going to inject or water medicate? Am I going to use a food animal drug or, in some cases, in the rare case, a non-food animal drug? Am I going to use it according to label or so-called extra label? If I go in with an injection or a water medication, am I going to follow up with feed medication or am I just going to stop? And lastly, if I do switch to a feed medication, when am I going to stop medication. So that is the steps that a veterinarian will go through.

(Slide.)

DR. MORRISON: Just very quickly, the first decision. Well, is it three pigs out of 1,000 or is it 250? So, if it is 250, I am probably going to have to go in and water medicate because I won't get very good compliance on injection.

(Slide.)

DR. MORRISON: The route of choice is always going to be to choose a drug labeled for food animals that contains the proper ingredient. It is always going to be your first choice.

(Slide.)

DR. MORRISON: And then you are going to -- if you have got this drug in the proper dosage form, as labeled for the indication, and I believe it is clinically effective, I am going to use it according to label.

(Slide.)

DR. MORRISON: If not, if not in the proper dosage form, it is not labeled for indication and I don't think it is clinically effective, I go to extra label. Where I require these criteria I have got to have a veterinary/client relationship. I have got to know these pigs. In a way, I have got to be personally responsible and I have got to be available.

I have got to sufficient scientific information to insure an adequate withdraw, I have got to be able to preserve animal or group ID and I have got to have records and labels.

(Slide.)

DR. MORRISON: In the rare case where we can't go this route, we are going to use a non-food animal drug where it is not prohibited, and again, very importantly, where I have got enough evidence to give a valid withdraw time.

(Slide.)

DR. MORRISON: Dennis covered this briefly. When do we medicate in the feed? Well, why would we? We would because it gives us the broadest coverage of the population at risk. I can medicate them all very easily. It is very labor efficient, it is very simple and it may be the cheapest program.

But why don't we always just go in and medicate with feed then? Well, it is probably somewhat difficult to achieve therapeutic levels in sick pigs. Sick people don't eat, sick pigs don't eat, and so they are not going to get the medication that we want them to get.

There is the potential for contamination of other feeds. Some pigs that are not sick will receive the medication. We don't want that. They are at risk, but it is kind of a waste, unless they are going to get sick without it.

And in some cases, just as it may be the cheapest program, it may be the most expensive program. So you are always, as a veterinarian, going to be weighing this. What is my treatment program?

(Slide.)

DR. MORRISON: I did a brief -- just a little survey in preparation for this meeting, and I asked some veterinarians, and I was quite impressed with their awareness and compliance with the guidelines. Some of these veterinarians have very detailed treatment protocols for clients.

They told me that they choose their product selection based on effectiveness first and cost second. And remember, this effectiveness is going to be their clinical perception in many cases and based on historical experience.

For some of them I saw some very elaborate spreadsheets for comparing drug costs and routes of delivery.

Generally, they will go between 10 and 20 percent as their cut off for whether they are going to go for injection versus water. Feed medication was generally used for chronic or preventive situations. And lastly, I saw a nice spreadsheet for cost effectiveness of growth promotants.

(Slide.)

DR. MORRISON: The last slide. I think it is important to recognize that within our industry I showed you an example of a 1,000 pig barn. We could go and I could take you to some barns that are not, in my view, well run. And I could take you to some other barns that are incredibly well run.

And so, in our industry I think of health management as being on a continuum, and you have got some farms out here that don't have good health and you have got some farms out here that have extremely high health. And when you look at sort of the descriptors of a low health system or a low health farm, you will find that -- this is probably more detail than you need, but they will have multiple sow sources feeding in. So it is just like that daycare facility.

If you have got 50 kids in a daycare, they are going home every day to 50 different homes and bringing back

200 bugs the next day. Okay? So multiple sources just creates a wonderful environment for disease to transmit versus one source.

Again, I won't go through any details, but all of these are descriptors of a poorly run management system. And you come over here and all of these are nice. We know, from experience, that those are going to be well run barns if they can do these sorts of things.

(Slide.)

DR. MORRISON: Now, if you could look at the whole industry out there, you can imagine that there is going to be sort of a bell shaped curve or normal distribution of health, and the majority of them are going to be somewhere in the middle. And we will have a few out here that are really well run, and we will have a few out here that are really poorly run, and these are the ones that are real challenges.

(Slide.)

DR. MORRISON: The challenge for us as veterinarians -- this is a fancy graphic now -- is to take this and move this curve in the right direction. So it is a continuum. It is important to recognize that health management out there is a continuum. We, as veterinarians, are trying to move everybody over to the right, and it is all sort of process that we are moving in.

And I am very confident. If I look back where we were 15 years ago -- I was in practice at the time -- I would liken a lot of those farms over there to low health farms. And I look at where what we work with today, and a lot of them are moving well over here. It is incredible.

And if I look 15 years from now, I am quite certain that we are going to be over here on this side of the graph as we continue to move farms off to the right.

(Slide.)

DR. MORRISON: I would just like to acknowledge that I did do this survey, and I appreciate the participation of these veterinarians who I contacted. I also used the AVMA brochure. And also, the AASP has a pharmaceutical issues task force that I am a part of, and I appreciate my participation in that group, Tom. Thanks very much for your attention.

(Applause.)

CHAIRWOMAN LATHERS: Thank you, Dr. Morrison. Are there any questions for Bob?

(No response.)

CHAIRWOMAN LATHERS: If not, we will now move on to our next discussion of antibiotic use in aquaculture, presented by Randy MacMillan. Dr. MacMillan is vice president of research and environmental affairs at Clear Springs Food, where he is responsible for the research and development program environment, stewardship and quality assurance.

He is the president of the National Aquaculture Association and the past president of the U.S. Trout Farmers Association. He is also the past president of the Idaho Aquaculture Association and the past president of the American Fisheries Society for Fish Health Session. He is the current chair of Minor Use/Minor Species Coalition. So, with that, we will now have a discussion of antibiotic use in aquaculture. Randy.

ANTIBIOTIC USE IN AQUACULTURE - AN OVERVIEW

By Dr. Randy MacMillan

DR. MacMILLAN: We are having to reboot. I am not promoting Microsoft. It just happens to be what is on this computer.

(Pause.)

DR. MacMILLAN: I represent a minor animal species group, and we don't have the kinds of resources that other sorts of people have, other sorts of animal industries have. When you think about minor animal species, it is important to understand why they are minor animal species. It is because not many of those animals are eaten.

And in aquaculture, which has been around for 300 or so years in the world, it is a very young industry in the United States.

(Pause.)

DR. MacMILLAN: So what I will do is go ahead and shut this down completely, and I will go ahead and start.

CHAIRWOMAN LATHERS: Please do.

DR. MacMILLAN: And then we will go quickly through some of these slides, once this boots up properly.

I think one of the big questions before this group is to what extent the antibiotics currently used or potentially used in U.S. aquaculture, and I really want to emphasize United States aquaculture and emphasize that throughout this presentation.

But, to what extent the antibiotics or potentially used in U.S. aquaculture contribute to increased morbidity or mortality, resulting from a reduction in the efficacy of a specific antimicrobial therapy of human disease as a consequence of antibiotic resistance by the bacterium involved in the disease process. And I have a slide that shows this.

But as I understand the purpose of this workshop or the task before us, it is to identify, with objective methods, how we are going to quantitate the risk. And I can tell you in United States aquaculture this is going to be a very formidable task, because there is considerable evidence, United States evidence, that the risk is so very low, in spite of some of the rhetoric that has gone on before us, before me anyway, about how dangerous aquaculture is.

Unfortunately, what has happened is people who have made those claims, those statements, are using aquaculture practices that are practiced in third world countries that actually dump human sewage and homothermic animal waste into those aquaculture facilities as a way to fertilize those facilities; to provide nutrients for algae that provide food for zooplankton that then provide food perhaps for the fish.

In the United States, that doesn't happen at all, and so, we have really gotten off the realistic track of what happens in U.S. aquaculture.

(Pause.)

DR. MacMILLAN: Okay. Here is my opening slide. Again, I wanted to focus on United States aquaculture, because it is so different than virtually any place else in the world.

(Slide.)

DR. MacMILLAN: I would like to cover what aquaculture is in the United States, what our basic culture methods is, because I suspect most people here have been acquainted with terrestrial animal agriculture. Very few of you are acquainted with aquaculture, with the growing of animals in the water.

I want to cover very briefly what we use antibiotics for, how we use them and, I might add, we only have two, two antibiotics that we can use in the United

States for food fish production.

What are our basic controls? That is, what controls do we use to insure the judicious application of antibiotics. And then I would like to, with whatever time I have left, talk about the potential public health risk and canopy measure in the use of antibiotics in aquaculture.

(Slide.)

DR. MacMILLAN: So, first of all, what is U.S. aquaculture? Well, it is a very diverse industry. The U.S. Agriculture Department recently completed a survey of aquaculture in the United States. The very first one was completed in 1998, and it identified 35 different species of aquatic animals that are raised in the United States; 35 species that they could identify or gather enough information on.

There is actually about 50 or so different species that are raised commercially under aquaculture conditions. Those species are raised in both fresh water and marine environments, and that becomes a critical issue in determining where risk might lie.

The species are raised under warm water conditions and cold water conditions, and that also is a critical factor in identifying where risk could occur or where potential risk is likely to occur. And as we go through the next few days, I would suggest to the participants that temperature and the type of water are going to be key factors that we need to look at.

We raise vertebrates and invertebrates. The vertebrates are catfish, trout, salmon, tilapia. The invertebrates are oysters, shrimp and crawfish, just as examples.

Crawfish don't use antibiotics. Nobody in the crawfish enterprises use antibiotics. Shrimp farmers in the United States should not be using antibiotics because they are illegal to use. Shrimp farmers in other countries might be using antibiotics. Catfish, trout and salmon producers do have two antibiotics that they might elect to use.

(Slide.)

DR. MacMILLAN: We raise food animals and non-food animals. A lot of non-food animals are imported into the United States in way of the ornamental fish trade. Sturgeon are raised, a very small industry for sturgeon, and then tilapia are raised. These are both food animals.

(Slide.)

DR. MacMILLAN: Again, at least 35 minor animal species raised in the United States. They are raised in various types of cultural practices. One of the most common is with the ponds. These happen to be catfish ponds from the Mississippi Delta. Those ponds are generally about three feet deep. They may be 20 acres in size.

In previous history, they were 50 acres in size. Harvesting upon that size is really a difficult thing, but 20 acres is more manageable. These same kinds of ponds may be used to grow shrimp on the coastal areas of the United States. We have a very, very small shrimp industry in the United States. There is much more shrimp produced in Ecuador and China and Thailand than in the United States. Far more.

(Slide.)

DR. MacMILLAN: Another culture method is with flow through systems. These are typically used for trout culture. These are earthen bottomed. This particular picture shows an earthen bottomed, earthen sided pond. They may be cemented ponds. The raceways may go from one raceway to the next to the next. The water is used repetitively. In this case it is not.

The water quality requirements for the animals raised in this type of aquaculture condition are far more stringent than those in the pond aquaculture conditions, and that is another key factor in identifying where the risks might come in aquaculture practices.

The water in these systems goes through very rapidly. Frequently the water right requirements are that you cannot consumptively use the water. It has to go in and out; in and out. In catfish aquaculture you can use the water consumptively, and so those ponds are typically static ponds. Water exchange doesn't occur.

Again, those aquatic animals don't require the same level of environment, environmentally stringency, that these colder temperature animals require.

(Slide.)

DR. MacMILLAN: And then, net pens. Net pens can occur in -- this is where they have a netted area for the aquatic animals to be placed and they are fed there. It can occur in fresh water ponds, in rivers and most frequently in the ocean.

Much of the salmon production in the United States, and certainly elsewhere, occurs in net pens in estuarine and in ocean areas.

(Slide.)

DR. MacMILLAN: There is a small type of system that is being looked at. There is really not any commercial production yet, although people have been in it for just a few years. But it is with closed recirculating water systems. Mostly fresh water systems that replace some of the water daily, and they discharge a small but concentrated eflon (sic.)

(Slide.)

DR. MacMILLAN: So, antibiotics in U.S. aquaculture. In the United Sates we have two. In other countries there are far more antibiotics available. In

Japan, for example, there are 29 antibiotics available for aquaculture. In the United Kingdom there are four. In Norway there are eight. In Chile, anything goes. In Ecuador, anything goes. In China, anything goes. They don't have the same regulatory framework in those countries that we do in the United States.

(Slide.)

DR. MacMILLAN: So the two drugs that we have available in the United States for food animals only is oxytetracycline and Romet-30. Oxytetracycline has been around for, I guess, 30 years or so. Romet-30, a potentiated sulfonamide, has been around since about the mid '80s. No. Mid '70s to '80 or so. For very few types of aquatic animals, and it is only in the feed.

We raise fish in a very intensive way. They are in the water, so they are not very accessible. The only way we can deliver an antibiotic or any other kind of drug, in a purposeful way anyway, is in the feed. There are some water treatments, but those are not antibiotics that are used for the water treatments.

(Slide.)

DR. MacMILLAN: The NADA is for catfish, salmonids and lobsters only. They each have a pretty long withdraw time of 21 to 30 days. The lobster is for the treatment of gaff kemyia. For catfish and salmonids it is for the treatment of modal --- septicemia, a specific disease of fish caused by erramonis hydrofla for example. And then for catfish it may sometimes be used for enteric septicemia of catfish, although that is not on the label.

(Slide.)

DR. MacMILLAN: The other antibiotic that is available is Romet-30, the potentiated sulfonamide. For catfish there is a three-day withdrawal time, and this is specifically for the treatment of a disease called enteric septicemia of catfish, ESC. There is a three-day withdrawal. And here, Romet is for the treatment of furunculosis. There is a 42-day withdrawal time.

The reason for the difference in withdrawal times is that with the catfish, when they are processed, the skin is removed and this particular antibiotic can concentrate in the skin. With the salmonids the skin is left on. So there is a much more protracted withdrawal time.

The interesting thing with Romet 30 is it is hardly used in either industry anymore. With the salmonids it never was particularly valuable because of the long withdrawal time. With the catfish they found alternate ways to manage that particular disease.

(Slide.)

DR. MacMILLAN: One of the things about aquaculture in the United States is that we don't use antibiotics as growth promotants. Never have, and I can't envision ever doing it for two reasons. One, it is very expensive. But number two, it doesn't work. At least not in fish.

We have done some research in my previous history at Mississippi State. We looked at antibiotics in a research situation to see if we could promote the growth of catfish. It didn't work. I am not aware -- and I am fairly familiar with U.S. aquaculture. I am not aware of anybody in the United States that uses antibiotics as growth promotants.

(Slide.)

DR. MacMILLAN: And there are several reasons why it doesn't work. The most important thing is that the bacterial flora in poikilothermic animals is itinerant. There is no resident flora. Whatever the fish or shell fish is eating, that is what will be in the GI tract of that animal. Or whatever is in the water.

If you take a catfish in cold temperatures and don't feed them, their gut, their GI tract, will essentially go sterile. There is no need for the bacteria there. It is sterile. If you change the water quality of the fish, that bacterial flora that you might recover will change.

Poikilothermic animals in aquaculture has what I would call several natural barriers to the transmission of antibiotic resistance factors or the occurrence of human pathogens in their system. One is that there are some basic physiological differences between cold blooded animals and warm blooded animals.

Those differences become very important when you look at the potential pathogenicity of bacteria. It is very difficult, for example, to take salmonella typhimurium that you recover from a catfish or a tilapia and infect a mammal with that bacteria. There appears to be some sort of biological adaptation, microbiological adaptation, that has to occur before that bacteria can cause disease of any kind in a mammal.

(Slide.)

DR. MacMILLAN: There is also some basic temperature differences. Cold blooded animals are just that, they are cold blooded. So the culture conditions vary anywhere from say nine or so degrees centigrade, up to 30 degrees or so centigrade.

Most of the bacteria that we are concerned about thrive not at those colder temperatures, but at the warmer 30 degrees and above type temperatures.

(Slide.)

DR. MacMILLAN: If you look at -- and I am not a food scientist or a food safety expert, but I went through some food safety text and look at the growth parameters or growth conditions, optimal growth conditions anyway, of some of the bacteria that we are perhaps looking at here.

Camplyobacter jejuni, no growth at less than 30 degrees centigrade. Salmonella species, there is a whole complex of salmonella species, the optimal growth is at 37 degrees. That doesn't mean it can't happen at a cooler temperature. It could. But the optimal growth is at 37. E. coli, 37; shigella, 37; vibrio, 20 to 30 degrees centigrade, but that is strictly a marine type bacteria.

Forsinia (sic) enterocolitica has a pretty good temperature range, as does lysteria monocytogenes. The warmer the temperature those, even for those bacteria, the faster it will grow. None of these bacteria infect fish. They may occur, but they don't cause disease in those fish.

(Slide.)

DR. MacMILLAN: There is also no resident microbial flora on the fish. As I mentioned earlier, the bacteria that are in the water at the time, that is what is going to be on or in the fish, the GI tract of the fish. Okay?

There is also a very, very large water dilution effect. If you think of raising fish in the ocean, just think how big the ocean is. In most, but not all, aquaculture situations that are profitable, they have a large volume of water at their disposal. That is going to cause a tremendous dilution effect in real life, and that has an impact or potential risk.

There is a limited human aquaculture fish environment interaction where people don't usually get into the water to be with their farmed animals. It can happen, but it is usually by accident.

(Slide.)

DR. MacMILLAN: There are certain management practices in the United States that also limit the potential for bacteria to get into humans from the aquatic environment or for resistance factors, plasmids, for example, to get transmitted on up the line. One, we use clean water.

The World Health Organization, about 10 years ago, estimated that about -- let me see -- two thirds of the world's aquaculture was produced in environments where human sewage and homothermic animal waste were purposely put into the ponds or rearing environments for fertilization purposes. Two thirds.

In China alone, which produces about 65 percent of all the aquaculture in the world, they still do that. They are changing. They are getting away from the human waste, but they are still doing the homothermic animals. The poultry, the pigs and whatever else. That still goes into aquaculture situations.

In Israel and in England and the UK, the placement of animal manures into those aquaculture environments goes on. In the United States that doesn't happen. That has a dramatic impact on the types of bacteria that are present, and hence, a dramatic impact on the relative risk of an aquaculture practice.

(Slide.)

DR. MacMILLAN: There are very, very few icthyozoonoses associated with aquacultured fish. Those that have been suspected are of an international flavor. For example, in Ecuador. There has been a suggestion that shrimp were the source of an antibiotic resistant vibrio cholera. Well, Ecuador, in all due respect, their waste management practices are not nearly as good as we have in the United States. Just their basic waste management practices.

Another place is in Japan where they -- in this particular case it was because they were eating live fish. And then one is in Israel where somebody got spined from a live fish and they perhaps got exposed to a vibrio that caused -- actually caused a mortality.

We have very, very few food-borne pathogens associated with aquaculture fish. The FDA, in 1998, did a salmonella survey of seafoods, wholesale seafoods, and seafoods, in general, had about the same cleanliness, if you will, as red meat products. Red meat products.

About two and a half percent of the seafood they tested, in a global sense, had salmonella recovered. The catfish, which were all domestic aquacultured catfish, had about 10 percent salmonella identified. Tilapia, about six percent. These were imported tilapia, not those raised in the United States. And then shrimp that were also imported in the United States, and they had about two and a half or so percent.

The MPNs, the most probable numbers for those, in all those cases was very low. We are talking .004 to .022, the most probable numbers for salmonella recovery, meaning that there are very few bacteria present. The place where they found a lot of bacteria was in wild harvested shrimp from India.

(Slide.)

DR. MacMILLAN: Another challenge to identifying the risk associated with aquaculture is that we are so diverse. We are all minor animal species, so human consumption patterns are going to be very difficult to track.

Another real complicating factor and something that has probably promoted some misunderstanding about aquaculture's role, or potential role, in the antibiotic resistance issue is that there are bacteria that grow under aquaculture environments without any antibiotic exposure who are resistant to the antibiotic, and it really becomes important then to track and identify the causes of antibiotic resistance.

Is it something that is transferable or not? In this particular case it was not transferable, but it is a very prevalent finding. It appears to be associated the -- in certain aquaculture environments with a highly nutritious environment, not with antibiotic exposure.

So it is one of the complicating factors that we are going to have to look at as we move forward in identifying ways to identify risk.

(Slide.)

DR. MacMILLAN: The pathogenic potential of most aquatic bacteria is low. It is not to say that they can't be made pathogenic. They can be made pathogenic. But it takes several passages through a mammal before they can become pathogenic.

The microbial flora in the GI tract is itinerant, as well as on the skin. The measures of resistance that aquaculturists and bacteriologists that have looked at this in the aquatic environment -- they have different measures of resistance internationally, and that is a real problem in terms of identifying what the real risk is.

It is possible, under laboratory conditions, to demonstrate plasmid transfer from fish pathogens to potential human pathogens. You can go the reverse as well. Human pathogens can transfer plasmids to fish pathogens under laboratory conditions. What we don't know is what the probability of that happening is, and I would suggest to you that 99.9 percent of the time it is a very, very low probability.

(Slide.)

DR. MacMILLAN: So how do we measure? In large respect, the issue, in my view, for aquaculture comes down to how do you measure the environmental impact of antibiotic use in aquaculture? How do you measure the environmental impact? And that is also going to prove to be a very difficult thing.

(Slide.)

DR. MacMILLAN: There is a cascade of things that has to happen for an antibiotic that is given to a fish to treat a specific disease; that has to happen in order for that to eventually have an impact on a human pathogen. It has got to go through the fish, it has got to be excreted by the fish, which a large part of antibiotics, the two that we have, can be excreted by the fish.

It has got to get into the water column, into the sediment, into the bacteria that are present in the sediment or the water column, and these are mostly aquatic bacteria that won't effect people, and then it has got to get a plasmid.

For example, it has got to get transferred from the sedimentary type of bacteria to the terrestrial type of bacteria and then, from there, into a human and then, from there, to cause disease and then it has to be a type of bacteria that is resistant to a particular antibiotic that a person would use. Quite a cascade.

What that means though is that it is going to be very difficult to quantitate the probability of that happening. I would suggest to you that the use of antibiotics in U.S. aquaculture has an undetectable impact on the prevalence of human pathogenic bacteria resistant to bacteria.

There is an overwhelming bit of qualitative data that supports that contention. There was a report put out in 1997 by a couple of scientists from the United Kingdom entitled, "The Use of Antimicrobial Agents in Aquaculture." It is a report to the Advisory Committee for the Microbial Safety of Food, the ACMSF working group on antimicrobial drug resistance.

In this report they shared the same opinion that I do about the relative risk of aquaculture. It is very, very low. It is not impossible, but it is very, very low. What they identified as the greatest risk is with the use of antibiotic in ornamental fish. That is where, from their view, there is the greatest potential for the transfer of resistance from the fish to people.

The one last thing is that relative risk is going to be dependent on water temperature, the species raised and the presence of human or animal waste. Thank you for your forbearance.

(Applause.)

CHAIRWOMAN LATHERS: Thank you. We will now take a break, and, please, be back here at 10:30.

(Whereupon, a brief recess was taken.)

CHAIRWOMAN LATHERS: I think it is time to begin. We have now completed our discussions of antibiotic use in ruminants, poultry, swine and aquaculture. We will now begin the next session with a discussion of antimicrobial drug discovery and development by Dr. Jeffrey Watts.

Jeff has a BS in microbiology and a master's in microbiology, both earned at Louisiana Tech University, and he tells me that as of just February 15th he has completed successfully his Ph.D. dissertation defense. Congratulations, Jeff.

(Applause.)

CHAIRWOMAN LATHERS: That was in biological sciences, and he has earned this at Western Michigan University. He is presently a clinical research scientists too in worldwide product division at Pharmacia and UpJohn Animal Health in Calamazoo. Jeff.

ANTIMICROBIAL DRUG DISCOVERY AND DEVELOPMENT

By Dr. Jeffrey Watts

DR. WATTS: Thank you, Dr. Lathers. What I am going to do over the next few minutes is talk about antimicrobial discovery in animal health, and particularly, I am going to talk about the impact of the resistance issues on discovery programs in animal health.

(Slide.)

DR. WATTS: What I am going to do is briefly frame up the resistance issues, then I am going to talk about the antimicrobial discovery programs, starting with the human programs and moving into the animal health programs. It is essential to do it this way because the animal health programs, as you will learn, very much live at the knee of their parent.

Then we will talk about the issues that effect antimicrobial discovery in animal health, what I call the environmental factors, the impetus to move away from broad spectrum compounds, the impact of the framework document; should we move toward vaccines, the other things that the antibacterial support groups do in animal health companies, including service support activities, and then wrap up with some comments on the future of discovery in animal health.

(Slide.)

DR. WATTS: Just to briefly frame this, as you know, the emergence of resistance organisms in human and veterinarian medicine is of great concern. The more resistant organisms tend to be predominantly those nosocomial in humans, with the veterinary contributions primarily through zoonotic pathogens.

There have been short-term responses to these issues, and these include things like the development of use guidelines, the development of formularies and therapeutic guidelines and restricted uses of selected compounds.

(Slide.)

DR. WATTS: When you talk about discovery, you are looking more than two to three years out. You are looking usually at seven to 10 years out. So what are the longer term effects, looking at 2005 and beyond? Will the antibiotic resistance issues prevent the introduction of new antimicrobial agents in food animals? That is the key question.

Will companies chose to stay in the food animal markets or in animal health at all? And will clinicians have therapeutic options for current pathogens or for new emerging pathogens?

(Slide.)

DR. WATTS: Let's talk a little bit about the human discovery programs. The cost of developing a new compound is very high. The estimates for a new human use antibiotic are $125 to $350 million. I have heard estimates on some of the newer compounds of more than $500 million.

The time it takes from the time that compound is initially discovered to the time it is introduced to market is 10 to 12 years; however, the markets tend to be quite large, or can be quite large, with markets easily being $500 million and several compounds making over a billion dollars per year.

(Slide.)

DR. WATTS: Over the last few decades there has been several strategies for countering resistant organisms. These are what I term, for the most part, incremental improvements. It is improving existing structures.

We have seen this happens with beta-lactams and various generations of cephlosporins, the fluoroquinolones, the antibiotic inhibitor combinations, what I call re-trading of older compounds, things like the amoxocillin clavulanate combinations, which can be quite successful. Augmentim, at its peak, I believe sold over $2 billion a year worldwide.

The problem with these types of strategies is the resistance mechanism. The basic mechanism is already in place, and all it takes is a minor modification by the organism to ramp resistance back up. So optimally, what we should do is screen for compounds with new mechanisms of actions.

(Slide.)

DR. WATTS: And so, our classic screening program involved a streptomycetes type of fermentation. We would then screen for inhibitory activity. We would discard any hits here if there was not activity, or we would discard if there were no hibs, no activity or any hibs that turned out to be nuisance antibiotics.

If it was active, if it appeared to be unique, then we would go through a re-fermentation process. The activity would be confirmed. We would scale up the chemistry efforts, we would identify the structure, then we would chemists at it into a synthetic chemistry program to develop new analogs.

(Slide.)

DR. WATTS: In the '80s this system collapsed, and the reason it collapsed was we had over 6,000 antibiotics and the system we used could not recognize new structures. Also, the antibiotic business was changing. There were only a few mechanisms of action. The customers were becoming rather disgruntled. They could only stand so many third generation cephlosporins being introduced into the marketplace, and there was also a question of whether or not they even needed new antibiotics.

(Slide.)

DR. WATTS: So the current paradigm is that now what we are doing is we are using a molecular target. This is targeted as our mechanism of action. We clone and express this target, we devise an assay, we now screen chemical libraries and natural products through this assay, we then select our lead compounds, and again, we throw chemists at it into an analog to develop usually thousands of analogs to screen from, and this is what has been termed a mechanistic screening program.

(Slide.)

DR. WATTS: And through the older techniques of incremental improvements -- and we are starting to see some of the -- at least adding components of mechanistic screening programs. We are seeing a variety of compounds come to market in human medicine.

We are seeing the broader community use agents, which include the extended spectrum fluoroquinolones, the glycosides; we're seeing macrolides, particularly the azolides. The ketolides are in development and moving through the pipeline.

We are also seeing narrow spectrum compounds primarily focused on the very resistance organisms, such as the enterococci and resistance -- staphorius, the improved glycopeptides, synercid, the everninomycins and the oxazolidinones represented by ---

(Slide.)

DR. WATTS: So let's talk about the animal health markets. The animal health markets tend to be much smaller than the human health markets. Generally, they are about one tenth in size. They are usually split among various animal groups, and these animal groups have varied use practices and preferences.

Multiple indications are usually necessary in order for a compounds to be successful in animal health. And because of these multiple indications and varied use practices in preferences, there has been a preference toward broad-spectrum compounds in most areas of veterinary methods.

However, as I said, animal health companies live at the knee of their parent. The parent company is relied upon for large scale screening, the chemistry efforts to expand the template, the initial in vitro toxicity screen, in vitro activity and toxicity screen, and even if you don't work in a class that your parent is working in, you still rely heavily upon them for things like path/tox services, formulation, pharmacokinetics and manufacturing production. You live in their infrastructure.

(Slide.)

DR. WATTS: So the way the process would work is that we would develop a target compound profile. We would probably look at a large single market for the first indication. We would have to define what that market would look like seven to 10 years in the future. We would have to know what our current competitors are, and we probably have some ideas of what other compounds are in the pipeline that will be our future competitors.

And we have to know the compound attributes, particularly those that give us a competitive advantage. And if you look at BRD as an example here, in the 1980s we were driven by residues. We saw ceftiofur come to market with no withhold. In the early 1990s this was changed into a convenience issue where we saw tilmicosin become a dominant player

And so the question becomes, as we head into the 2000s, will resistance become a dominant issue and a competitive advantage?

For the most part, the animal health discovery companies obtain their lead compounds from the human health program. We also look at the available in vitro activity and toxicity data, usually using a human organism as our veterinary surrogate.

For example, of course, you look at data for E. coli. What you would look for, if you were interested, is does this culture have pestoral activity. I would look at H Flu data. Does it have streposis activity? I would look at streptococcus pneumonia data. So you are making that transition from those human pathogens.

You would screen for activity specifically against your veterinary pathogens. These would be in vitro screen, MIC determinations, you would then screen through various mouse models, target animal models and you would like for demonstrated efficacy and safety at this time.

At this time you would transition to development, and this is where the discovery scientist plays a key role, in that usually the discovery scientist has to be an advocate for its compound, and they are responsible for successfully transitioning those compounds from discovery into development.

(Slide.)

DR. WATTS: If we look at the compounds that are currently available and the programs they came out of, Tilmicosin came out of a animal health program. The ceftiofur, pirlimycin, enrofloxacin and chloramphenicol originally arose out of large corporate screens for compounds to be used in human medicine.

This was the year of the first publication on these articles, and one of the things you need to keep in mind is if you see ceftiofur at 1987, that means that compound was originally looked at in about 1980. If we look at florfenicol at 1980, that means the screen for that compound was probably in the mid '70s.

Pirlimycin, lincosamides, in 1985 first described. I can tell you that the lincosamides screen for pilimycin was discovered in the mid '70s. So, when you start talking about new compounds that you would just introduce, many times those compounds are 10, 15 or 20 years old.

(Slide.)

DR. WATTS: So the question becomes -- is as we see the mechanistic screening programs kick in in human medicine, as we see new antibiotic and new antimicrobial classes with new mechanisms of action being introduced hopefully over the next 10 years, then will animal health be allowed to participate and be able to participate in this revolution.

So one of the things that we need to look at are the environmental factors. Again, the changes in clinical use patterns, the argument over whether or not we should be developing narrow versus broad spectrum compounds, the regulatory environment, particularly the framework document, and prevention strategies. Should we move to just vaccinations and that becomes our dominant way of controlling diseases and they replace antimicrobial agents?

(Slide.)

DR. WATTS: There is an excellent talk at ICAC this year by Dr. Bob Mollering on the argument of narrow versus broad spectrum compounds in human medicine. Narrow spectrum compounds target a given class of organisms. Usually gram positive or gram negatives. They target a specific genus or species even, while broad -- the definition for broad tends to be less defined.

We usually know a broad spectrum compound when we see it, in terms of the type of spectrum it covers, but most people think of broad spectrum compounds as those that cover both gram positive and gram negative organisms.

(Slide.)

DR. WATTS: The advantages to a broad spectrum compound are that if you have an unknown etiological agent, you can cover it or have a better chance of covering. You can cover polymicrobial infections, and it provides peace of mind for the clinician.

The disadvantages are that there is a greater impact on normal flora, what is called the innocent bystander effect, selection of resistance in multiple species of organisms and it may impart a false sense of security to the clinician.

(Slide.)

DR. WATTS: The advantages of narrow spectrum are you have reduced selection for resistance, it is targeted against selective pathogens, and you have a reduced innocent bystander effect. The disadvantages are you need a precise diagnosis, and it cannot be used to manage polymicrobial infections.

(Slide.)

DR. WATTS: This is the way Dr. Mollering summed up his talk, and I think it is the best way I have seen of summing up the argument of narrow versus broad. "Narrow is good, if you can live with it, and broad is bad, unless you need it."

(Slide.)

DR. WATTS: So, should animal health companies focus only on narrow spectrum compounds? The thing we have to realize is that it will require more compounds in the portfolio. That is, a company, instead of living on one or two compounds, now has to manage two, three, four and five compounds.

You are going to have to have multiple classes of compounds, and that is difficult to do if your parent program is heavily invested in one class. So you are going to have to go outside your company in order to find additional classes.

You have to provide support for each compound. Support means path/tox, formulation, manufacturing, marketing. You will have limited indications for each compound and limited label expansions. The problem you also have is that marketers will tell you there is difficulty marketing narrow spectrum compounds, particularly in markets where there are broad spectrum agents available. In a market where there is a narrow and a broad, the broad always wins and always dominates the market.

(Slide.)

DR. WATTS: The regulatory climate at this point in time primarily revolves around the framework document, and I have tried to summarize the categories here, with category one being the compounds considered essential for treatment of serious or life-threatening disease in humans.

Category two is important for treatment of serious disease, but alternative therapy exists, and category three is limited or no use in human medicine.

(Slide.)

DR. WATTS: What is the impact of a framework document? Short-term, category one blocks animal health development for new classes in food animals. Group two limits development to those indications with low risk of resistance development, and category three will limit compounds to those of low potency, toxicity problems or high levels of resistance in human pathogens.

This links the veterinary use to the human use in terms of both availability of drugs, particularly availability of drugs in human medicine to treat specific infections, and the resistance levels in human pathogens.

(Slide.)

DR. WATTS: Another thing we have been told is we should explore vaccines as an alternative to antimicrobial agents. I believe that vaccines are important and they are an important component of disease management programs. They should be used when and wherever possible. I think prevention is the key.

However, vaccines may not replace antimicrobial agents, and the reasons are that effective vaccines are difficult to develop for many bacterial pathogens. They target only one agent or one, so you have to have a multivalent vaccine.

One of the things that we have very little information about, but something that may be important, is that vaccines are a selective pressure. They may change pathogen distributions and they could change pathogen distribution to a more resistant pathogen. We just don't have a lot of information on that.

Vaccine market cycles are shorter and the vaccine value tends to be much lower. That is, because the cost of vaccines tend to be much lower than it is for antibiotics, those market values tend to be much lower. You tend to have to manage many more vaccines in your portfolio in order to get the same value that you would for one single antibiotic. This is truly on example where an ounce of prevention is not worth a pound of cure.

And also, one of the things that may be required is surveillance of effect on pathogen distribution. It may be necessary in order for us to understand what is going on in these various management systems.

(Slide.)

DR. WATTS: The service support activities. This is what I jokingly refer to as what your discovery people do in their free time. Most microbiology expertise in animal health companies reside in the discovery program. Usually more than 50 percent of their time and resources are spent in this area each year.

You have to remember that most of these groups are fairly small. A group with 10 to 15 people would be considered quite large for a dedicated antimicrobial discovery program in animal health.

And these are sort of the things that they do, the activities that they may be involved in: Generating MIC data for label expansions and extensions, conducting MIC studies or in vivo to meet regulatory requirements, a lot of the resistance monitoring efforts reside in the discovery group, and also, susceptibility test development to support those compounds. As resistance needs and monitoring needs have ramped up, that is taking time away from discovery efforts.

(Slide.)

DR. WATTS: So what is the future of animal health antimicrobial discovery compounds? The compounds currently in development will probably be the least effective. They will probably make it to market with some sort of indication. It may be a limited indication at first.

Many of these programs will be re-focused onto the companion animal markets because the resistance issues have not been as great a concern there. The food animal markets will be limited to those with reduced resistance concerns.

The availability of new compounds and the decreased utility of existing compounds in human medicine may allow the use of some of the newer classes of antibiotics in food animals, but that is a longer term scenario. And the gap in food animal compounds will begin to occur about 2005, unless directed efforts in this area remain in place.

(Slide.)

DR. WATTS: In order for this to happen, one of the things that the animal health companies have to do is their management has to have the resolve to stay in the game, and they have to have the resolve to make sure the programs are adequately resourced.

Discovery programs must build in resistance as part of the target compound profile. That is essential. And so we would do things like mutation frequency studies, resistance mechanism determinations, dose/use patterns that minimize resistance, and I will guarantee you that as new compounds come to market that are safer in terms of antibiotic resistance, that this will become a marketing issue once these compounds to the market.

I believe that wraps me up at this point in time. Questions?

(Applause.)

CHAIRWOMAN LATHERS: Thank you very much. Are there any questions?

(No response.)

CHAIRWOMAN LATHERS: Thank you again. We now move on to our next topic, antimicrobial new animal drug applications, a review process overview. Dan Benz will be presenting this.

Dan has earned a BS at the University of Illinois and a master's at Colorado State University. He has a Ph.D. in nutrition from Texas A&M University, and he is presently an animal scientist in the ruminant drug team in the division of biometrics and production drugs at the Office of New Animal Drug Evaluation at the Center for Veterinary Medicine. Dan.

ANTIMICROBIAL NEW ANIMAL DRUG APPLICATIONS

REVIEW PROCESS OVERVIEW

By Dr. Dan Benz

DR. BENZ: Thank you. You may wonder why I am here this morning. Well, I wondered that too. It is not because one Friday afternoon I was sitting around my office and somebody came in and said, "What are you doing the 22nd of February? Are you busy?" And I said, no. Well, they said, you can give a speech.

It is not because this was originally scheduled to be between 11:00 and 11:30 you would have lunch and somebody said, well, you can make it short and go to lunch early. It is not for all those reasons. The actual reason I am here today was that there was a request made that we tell John Q. Public just what is required to support an NADA.

You know, there is a lot of talk about putting a lot of additional requirements on the drug companies, so what is currently required? And that is what I am going to talk about today, and this is pretty much going to coffer all new animal drug applications, not just antimicrobial, and I will show you some differences when we get into those.

What are the contents of an NADA? Well, what supports an NADA? Well, the first thing we have is a cover letter from the sponsor. They are going to tell us what they want; a description of the request. We would like to get this compound approved for this type of animal, et cetera.

We have a lot of miscellaneous information, patent information, marketing exclusivity information that we tend to put in there. We have a FDA 356V. I am not sure what the 356V stands for, other than I assume it was the 356th numbered form that FDA had. I know the V does stand for veterinary.

That form is based on the regulations 21 CFR 514. If you want to look them up, that is where it is. A very important thing that I have bolded, underlined and italicized is it must be signed by a responsible official or authorized agent by the company. And if it is a foreign company, they have to have somebody in this country that has the authority to sign them.

(Slide.)

DR. BENZ: Now, for the quiz of the day. How many can read this? I know you can't, but we are going to talk about it in my ensuing slides. But I wanted you to see what an application looked like besides NADA. Drug product, some information here below, some instructions for use, Paperwork Reduction, a little spot for a doc unit to use. Also, it was nice to figure out how to use Adobe Acrobat and get it into PowerPoint.

(Slide.)

DR. BENZ: A little information on the back side. Some fine print. Every good form has got to have its fine print that you sign and don't know about. And a place for the signature and their title with the date.

(Slide.)

DR. BENZ: What is on the form FDA 356V? Well, one of the first things is drug product information, the established proprietary names. For example -- and I am going to stick away from the animal area so I can't get in trouble by particularly picking anybody's product out.

Acetaminophen. Tylenol in the human area, the established proprietary. Advil, Ibuprofin. So there is a couple of examples.

Dosage form. What form will that be? Will it be an injectable? Will it be an oral in the feed? So we want to know what type will be used up front.

Proposed indications for use. Whether it is going to be a production or increased average daily gain, increased milk production, you can go down that, or some therapeutic use. The species of the animal that it will be used in: Cattle, swine, sheep, goats, horses, dogs, cats; whatever. And its proposed marketing status, whether it is going to be prescription or over-the-counter.

And I suspect, some time when this is updated, it is going to have three prescription OTC in for the new class of veterinary feed directives. But right now we have two on the form.

(Slide.)

DR. BENZ: Some additional information. Applicant's name and address. We want to know where they are doing business. The type of application, whether it is an original or a supplement. Original means it is the first time we have ever brought it in. Maybe it is a new chemical entity. We have never looked at it before. A supplement is something that would be approved products already on the market and the firm is trying to make some sort of change to that.

A reason for the submission. What are you trying to do? The good old Paperwork Reduction Statements. We have to have that in there to be in compliance with our OMB regulations and Paperwork Reduction Act. And some instructions for submitting an NADA. How many copies we want, et cetera, are all on that form.

(Slide.)

DR. BENZ: As I said, that was on the second page. There is appropriate sections, and these sections are checked as necessary. I will give you a couple of examples which I will go into later. But you don't really have a need for human food safety in companion animals. So that section would not be checked.

Also with companion animals the environmental assessment is a lot easier. Lots of times they get a categorical exclusion. So those types of things may or may not be checked.

And I said the fine print. That is the legally binding statements. No one was debarred under the Food Drug and Cosmetic Act will be involved in any capacity. That came out of the generic scandal. And finally, a warning. A willingly false statement is a criminal offense. In my mind, that says FDA does mean business.

(Slide.)

DR. BENZ: We are going to go down the sections; right down the 356V. I know you couldn't read it. That is why we came to these slides. We have the identification of the compounds, table of contents and summary. Particularly the summary to describe the chemistry of the proposed drug so we know what it is.

Its clinical purpose. Again, whether it is therapeutic, a growth promoter. And the summary of the laboratory and clinical studies to support that application.

(Slide.)

DR. BENZ: Labeling. We have product labeling. It may be the labeling on a vial. If you also have any packaging that goes along with it. If a vial comes in a box and that has labeling, we want to know that.

Package inserts. If you go to CVS and pull out a tube of ointment and you have got an insert, we would also look at the same type of insert that would be available for an animal drug. And then, if it is a feed, we want to look at type A, B and C medicated labeling or the feed labeling.

The reason that we need the labeling, besides the fact that it will be put out for public display later on, is we also look at the labeling in conjunction with the safety and effectiveness to see if the two coincide, if the labeling is supported by the safety and effectiveness data.

(Slide.)

DR. BENZ: Okay. The components and composition section, a list of all articles used as components, the statement of the composition, a description of the fermentation of the antibiotic drug; some sense of how the products are made.

(Slide.)

DR. BENZ: Again, more on manufacturing methods, facility controls, the personnel that are involved, the facility equipment, a description of the drug synthesis, how it was made, raw material controls, manufacturing information.

(Slide.)

DR. BENZ: And additionally, finished product controls, stability program, container packaging, lot control number system. In a nutshell, how was the product made and can they make it again and come up with the same consistent product over and over.

And then finally, we have a way, with a lot control number system, et cetera, to monitor that product. You know, if some product gets out in the marketplace and it is recalled, you have to know where it came from, and that is where the lot control number system comes from. So we are looking at all -- the complete manufacturing process.

(Slide.)

DR. BENZ: Samples. We hand ask for samples upon request. We seldom do. I assume there must be a reason some time along the way that we have asked for samples. Examples that I could think of is if you had a question of is there an active ingredient in this drug or that type of thing.

And again, here is one that I said earlier that only applied to certain ones as applicable. Analytical methods for residues, only to food producing animals. Again, we would not look at looking for residues in companion animals.

(Slide.)

DR. BENZ: We have to have evidence of safety and effectiveness, and this includes human food safety, target animal safety, user safety, and again, effectiveness.

(Slide.)

DR. BENZ: Human food safety. We are looking drug residues in animal tissues. Those include meat, milk, eggs; you name it, what we could call as edible tissue. We look at acute toxic response. An example is what would happen, you know, to children who are allergic to peanuts, get a peanut and have acute response. They might go into convulsions.

We are also looking at those kinds of things with residues of drugs. What would be a short-term effect if they got a lot of the drug, and then a chronic exposure toxicity or a long-term exposure. What happens to them.

We also look, as part of that, antimicrobial resistance and pathogen load. Those have been called 558.15 studies, salmonella sheddings; they have gone by a lot of different names. Dr. Cooper is supposed to give that presentation next.

(Slide.)

DR. BENZ: Target animal safety. We have to have studies or reports to demonstrate the cumulative effect of the drug on the animals, such that the drug does not adversely effect the treated animals. Simply put, does the drug harm the animal? We are going to look to see if the drug harms the animal at all.

(Slide.)

DR. BENZ: User safety. We look at hazards associated with manufacturing; direct. Is there any hazards to the occupational exposure to site when the drug is manufactured. Indirect, such as manufacturing emissions; hazards associated with administration to animals.

An example might be that you have a product that is very safe in the animal, but if the human took and injected themselves by accident, it could be very toxic. So we want to look at that.

Hazards associated with the use of air, water and solid waste contaminated by use and disposal of the drug. An example that I could give you would be that if you have a drug that you give every day, if it is an injectable and you are giving it to 1,000 animals, what are you going to do with those 1,000 syringes? We look at those types of environmental concerns that go along with that.

(Slide.)

DR. BENZ: The effectiveness determined by experts, those experts such as myself by training experience. Must of us have various degrees. We have some experience in that field. That is what we are paid for.

We, again, fairly and reasonably concluded that the drug will have the effective reports or it is represented to have the conditions of use to prescribe recommended suggested labeling. As I said before, we are looking at the labeling and effective data and see that the two match and what is actually in the submission will support that labeling and will that product be used in the marketplace in a reasonable manner.

(Slide.)

DR. BENZ: The effectiveness is based on substantial evidence, and I won't describe what that is -- that would be a whole other presentation -- consisting of one or more adequate and well controlled investigations, such as a study in a target species, a study in laboratory animals, a field investigation, bio equivalent studies and in vitro studies.

And those would depend on what you were trying to do. You might have a model that would predict a disease condition. It might be appropriate with an in vitro study or a laboratory study. Some other types of study might not be appropriate to do that. So you would have to use what was appropriate for that condition.

(Slide.)

DR. BENZ: Another section is our GLP good laboratory compliance section. There is a set of regulations that tell you how you should collect data in a correct manner, such as data signed, dated, it has gone through a QA unit, a quality assurance unit. We feel pretty comfortable about it so that the firm has attested that they have collected the data that needs to be, such as target animal safety and human food safety under those conditions and have verified that.

Another section is environmental assessment or EA. The use, manufacture and disposal of that drug does not propose a significant environmental impact and an NADA must have an EA or a claim for a categorical exclusion. The categorical exclusion comes in for such things as companion animals.

Another example would be that you have a drug that is on the market. You are going to change the labeling to clarify something, but you are not going to change the overall exposure of the drug in the population. You might want to rename or reclassify the genus or a species of some antimicrobe.

(Slide.)

DR. BENZ: Our Freedom of Information summary. That is the information that is for public disclosure that we make available. That includes everything but proprietary information, such as chemistry and manufacturing; how the product was marketed.

That is available in the dockets manager branch or on our web site for anybody to look at. Such things that are in there are description of the effectiveness data that was used to support the application, description of the target animal safety, human food safety and there is a few other things. But that is the kind of stuff that we are looking at.

And then there is a section called "other" that I have never used, but every application has to have a good other just to catch everything else.

(Slide.)

DR. BENZ: Now, I told you what you find that the drug company or the sponsor submitted, but if you wanted to go in and look at an NADA and see what CVM has got in there, the agency? Basically, these are the documents that are in an NADA that we have generated.

Review. I generate animal science reviews. We have got people that generate veterinary reviews, human food safety. But our interpretation of the data and how it would support that application. We have gone and looked and this is my scientific review.

Sometimes we have meeting minutes or memorandum of conference. We may have had a meeting with the firm. We have sat down around a table and discussed issues and those issues are of importance, so we want to document in the field that we have had this meeting. Sometimes we have internal meetings with our supervisors or other colleagues. We want to document what happened there.

We have that and it goes into the file, so that if five to 10 years, if these types of questions come up again, we can look and say, well, this is what those types of decisions were based upon.

Sometimes we have a document summary, which is kind of a historical basis of where that submission is moved, what is going on, whether it is human food safety, effectiveness, target animal safety, but the status at the time. If the drug is going to be approved, we have a memorandum recommended approval, which is kind of obvious to the name.

That memorandum has a lot of administrative information. Basically it tells those in our supervisory chain, which in my case is Dr. Lathers, that I have dotted all the I's and crossed the T's and followed everything along the way and that approval is following our policies and procedures, and they can feel comfortable in signing off and saying, yes, we should recommend this approval.

And it is a great place for them to pick up and say, what is going on in this application; in a four to five page document and say this is all the history I need to know. Sometimes we have an administrative memorandum.

That administrative memoranda can be because the data didn't quite address a situation. We had some concerns, but there was a policy decision that set that aside. It could be policy decisions that came from above. So that is administrative memoranda.

A draft regulation. CVM drafts a regulation which eventually ends up in the Federal Register for approved products. That is in there. That is something that we also send forward. We try to provide what will end up in the CFR and the Federal Register; how we want it.

And then there are letters, letters to the sponsor that are necessary. Sometimes there is a really nice letter that says, dear company, your application is approved and you can begin marketing it. Sometimes we have letters that says please try again, these are the others that we would like some additional information and please come back and give us that information, and we will re-evaluate your request.

And, that is the end of my speech. Any questions?

(Applause.)

CHAIRWOMAN LATHERS: There is a question for Dan?

Dan, would you wait just a moment, please. Would you use the microphone, please.

MS. MELLON: Hi. My name is Margaret Mellon. I am from the Union of Concerned Scientists. From what I -- from what you have presented, there doesn't seem to be any information collected by the agency on usage. I mean, whether approved compounds are actually used, in what amount and in what animal systems.

Is that true? And if you don't get it in this process, do you get it in any other process?

DR. BENZ: There isn't any information collected here because this is the pre-approval process, and it would be hard for us to estimate how much would be used, other than there is some estimation in the environmental assessment because they have to have some idea of what kind of impact.

We have a whole office, the Office of Surveillance and Compliance, that looks at products post-marketing; whether they are used in accordance with label directions, how much there is used, et cetera, and that is their complete function, is surveillance and compliance.

MS. MELLON: Does the agency make that available in a report, like this is how much of a particular antibiotic that has been used in a particular system in 1998 so we could track it over time to see whether antibiotic use is going up or down in particular systems to get a better idea of exposure?

DR. BENZ: I really don't know the answer, because I am from the Office of New Animal Drug Evaluation. I do the pre-approval, and I am more on will the product be safe and effective. If there is anybody here from Surveillance and Compliance that could answer that -- or we can leave it for later today. I really don't know.

MR. : --- animal drug experience report.

DR. BENZ: Well, there is a drug experience report that would tell how much the drug -- each owner of an NADA that is approved must report to the agency annually in something called a drug experience report. It tells us how much the drug is used.

And I don't know if it is summarized across companies or anything in public made available, but we do have some indication --

MS. MELLON: We have tried to locate such reports and have never been able to do so. But if they are available, we would like to hear about it.

CHAIRWOMAN LATHERS: Dr. Thompson.

DR. THOMPSON: I am not from surveillance and compliance, but I will try to answer your question. We do get information, as you are probably aware, in the drug experience reports, but that is targeted specifically to the individual drug, and most of that is considered proprietary information.

There are some problems, which we have stated in the framework document, with how we currently collect the information, and we are in the process of trying to make some changes in terms of changing our regulations to provide a better basis for tracking drug usage information in the future and providing a better linkage to the resistance data that we are collecting through the National Antimicrobial Resistance Monitoring System.

The questions about how the information will be released publicly, we don't really have an answer for that yet. We are looking at that issue in terms of providing better public information in the future on that. But some of it is considered proprietary information and is not releasable by the agency.

MS. MELLON: Well, I do -- I am glad that the agency recognizes that it is a problem, and I guess I would just say that there are ways around proprietary information, aggregating data and all that, which I know you have thought about.

But I would just encourage you to go in that direction. It is a real hard issue to address, either from a health standpoint or a public policy standpoint, when you don't have any idea, really, of how much antibiotic is being used, where and what the trends are over time.

DR. BENZ: Well, I do know. I can't make a plug for them, but there is a commercial service that collects that data.

MS. MELLON: Well, it isn't very satisfactory either. Frankly, you know, being from the public interest community, I want information that has the kind of authority and credibility that would come from it coming from the government. That would certainly be our preference. Thank you.

CHAIRWOMAN LATHERS: Are there any other questions at this moment?

(No response.)

CHAIRWOMAN LATHERS: If not, thank you Dan.

Our next speaker has just arrived, and I think we will need a few minutes to load her PowerPoint slides. One announcement that I have been asked to make is that Bill Flynn is obtaining as many copies of the talks that we have heard this morning as possible, and hopefully, copies will be available for us this afternoon.

In addition, Bill anticipates that these will be on the home page at a later date. So you will have hard copies today and electronic copies in the future. Give us just a moment, please.

(Pause.)

CHAIRWOMAN LATHERS: Our next speaker is Jean

Cooper. Jean is a 1987 graduate of the University of Illinois Veterinary College. She does have a master's of science in dairy microbiology and nutrition, and an undergraduate degree in animal science, both earned at Rutger's University.

She is, at this time, chief of the clinical chemistry and toxicology branch at the Centers for Devices in Radiological Health at the FDA. In her current position she did work for the Center for Veterinary Medicine as an application reviewer. In this capacity she reviewed the studies supporting the 21 CFR 558.15 Regulation on the sub therapeutic use of antimicrobial drugs in food products. Jean.

"558.15" STUDIES: A HISTORICAL PERSPECTIVE

By Dr. Jean Cooper

DR. COOPER: Thank you. I had another meeting I had to be at earlier, so that is why I didn't make it here until now.

The Food and Drug Administration is the primary federal agency responsible for insuring the safety in food supply relative to the impact of drug use in food animals. The Center for Vet Med approves animal drugs that are effective and safe for animals and for consumers of animal products from treated animals.

CVM considers the properties of each drug in